



TITLE:

Kinetic Treatment of Kinetic Resolution of
Racemic Acid Anhydrides with Chiral Amines
(Commemoration Issue Dedicated to
Professor Eiichi Fujita on the Occasion of his
Retirement)

AUTHOR(S):

Kawakami, Yukio; Hiratake, Jun; Yamamoto, Yukio;
Oda, Jun'ichi

CITATION:

Kawakami, Yukio ...[et al]. Kinetic Treatment of Kinetic Resolution of Racemic Acid Anhydrides with Chiral Amines
(Commemoration Issue Dedicated to Professor Eiichi Fujita on the Occasion of his Retirement). Bulletin of the Institute
for Chemical Research, Kyoto University 1985, 63(2): 100-103

ISSUE DATE:

1985-08-24

URL:

<http://hdl.handle.net/2433/77102>

RIGHT:

NOTE

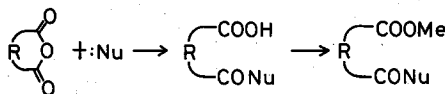
Kinetic Treatment of Kinetic Resolution of Racemic Acid Anhydrides with Chiral Amines

Yukio KAWAKAMI, Jun HIRATAKE, Yukio YAMAMOTO, and Jun'ichi ODA*

Received April 5, 1985

KEY WORDS: Stereoselectivity/ Kinetic Resolution/ Reaction Rate

In connection with our study of the stereoselective acyl-substitution of prochiral acid anhydrides using chiral nucleophiles or chiral catalysts, it became necessary to establish a facile method to determine asymmetric yields of the reactions. When chiral binaphthyldiamine derivatives were employed as nucleophiles, the diastereomeric excesses (de's) of the products were determined on the corresponding methyl esters by HPLC.¹⁾ On the other hand, the enantiomeric excesses (ee's) of the products produced in the catalytic nucleophilic ring-opening reaction were established by conversion of enantiomerically enriched half esters to diastereomeric amide-esters with (*R*)-1-(1-naphthyl)ethylamine using HPLC.²⁾ The scale of selectivity of asymmetric synthesis can be directly assessed by ee or de of the product.³⁾ In



kinetic resolution, the ee of the remaining substrate and the ee (or de) of the product depend not only on the ratio of the rate constants (k_A/k_B) but also on the reaction conversion and the substrate/reagent ratio. Mislow,⁴⁾ Kagan,⁵⁾ and Sharpless⁶⁾ reported the theoretical treatment of kinetic resolution. Among them, Sharpless presented a valuable equation to estimate k_A/k_B as a function of the ee of the remaining substrate and the reaction conversion. The similar method was also developed in the enzymatic system which was represented by steady-state kinetics.⁷⁾ However it becomes sometimes troublesome to determine the variables when a reaction is carried out with small amounts of reagents. Moreover, the method often requires isolation of the remaining substrate to determine the ee.

Now, we present an alternative approach to assess k_A/k_B when diastereomeric products are yielded in kinetic resolution. In a reaction of kinetic resolution,

* 川上幸夫, 平竹 潤, 山本行男, 小田順一: Laboratory of Plant Product Chemistry, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.



eq. 1

$$k_A/k_B = \ln ([A]/[A]_0) / \ln ([B]/[B]_0) \quad \text{eq. 2}$$

where A and B are enantiomers, C is a chiral reactant and D and E are product diastereomers, the above relationship (eq. 2) is derived according to Sharpless,⁶⁾ and $[A]_0$ and $[B]_0$ are the initial concentrations of respective enantiomers. When the chiral reagent C is consumed completely, the ratio of the rate constants is newly represented as

$$k_A/k_B = \ln (1 - 2R/N) / \ln (1 - 2/N + 2R/N)$$

$$= \ln (1 - 1/N - de/N) / \ln (1 - 1/N + de/N) \quad \text{eq. 3}$$

where N ($N > 1$) is the ratio of the amount of the racemic substrate to the amount of the optically active reagent, R is the ratio of the amounts of the product diastereomers, and de is %de/100 of the product.

In kinetic resolution of racemic acid anhydrides with chiral amines, the selectivity of the reaction was assessed according to the above equation. Racemic *trans*-2, 4-dimethylglutaric anhydride **1**¹⁾ was reacted with the axially dissymmetric diamine **2a**¹⁾ in the anhydride/amine ratios of 2, 3, 4, 5, 10, and 20. The diamine **2a** was consumed completely in 10 hr⁸⁾ in every run and the half acid obtained was converted to the amide-ester **3a** with diazomethane. The %de's of **3a** were determined on HPLC and are shown in Table 1. The ratio of the rate constants was calculated to be 9.2 by the least squares method. The (*R,R*)-anhydride **1** was proved to be attacked preferentially based on the chemical transformation of **3a** to (*2R, 4R*)-(–)-2, 4-dimethyl- δ -valerolactone.¹⁾ Racemic *O, O'*-diacetyltartaric anhydride **4**⁹⁾ was treated with (*R*)-1-(1-naphthyl)ethylamine (**5**) in the same ratios as **1** vs **2a**. The product amide-acid was also methylated to **6** whose %de's were determined by HPLC. The results are also presented in Table 1. A parallel experiment using (*2R, 3R*)-**4** and HPLC analysis showed that the *2S, 3S* isomer of **4** was consumed preferentially.

The acid anhydrides **1**, **4** and 2-phenylbutyric acid (**8**) were also submitted to resolution with the chiral amines **2a**, **2b**,¹⁾ and **5** in which the substrate/reagent ratio was fixed at 5. For activation of the acid **8**, *N, N'*-dicyclohexylcarbodiimide (DCC)

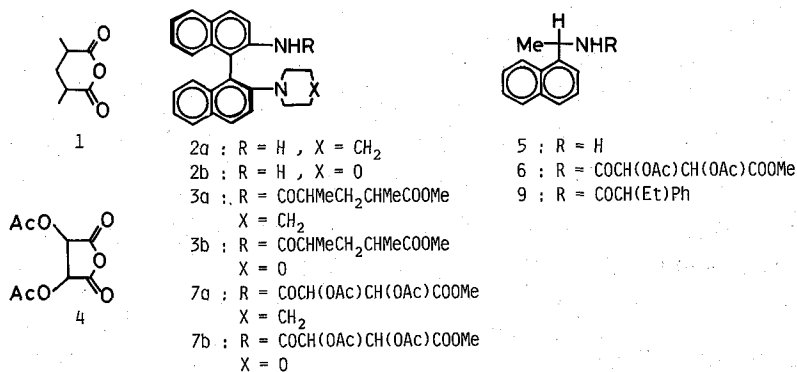


Table 1. The diastereomeric excesses at different substrate/reagent ratios and the ratios of reaction rates

acid anhydride	amine	amide-ester	reaction condition		%de at						k_A/k_B
			solvent	temperature	$N=2$,	3,	4,	5,	10,	20 ^a	
1	2a	3a	toluene	-20°C	64,	74,	76,	76,	80,	80 ^b	9.2
4	5	6	CH ₂ Cl ₂	-20°C	34,	34,	42,	44,	42,	44 ^c	2.7

a $N=[\text{substrate}]_0/[\text{reagent}]_0$ b Determined on HPLC; $\alpha=1.20$; eluent, hexane: EtOAc: Et₃N=7.5: 1: 0.05, flow 3.0 ml/min.c Determined on HPLC; $\alpha=1.20$; eluent, hexane: 2-propanol: Et₃N=10: 1: 0.5, flow 2.0 ml/min.

Table 2. The diastereomeric excesses at a fixed substrate/reagent ratio and the ratios of reaction rates

acid anhydride or acid	amine	amide-ester	reaction condition		%de at $N=5$	k_A/k_B
			solvent	temperature		
1	2b	3b	toluene	-20°C	68 ^a	6.2
4	2a	7a	CH ₂ Cl ₂	room temp.	0 ^b	1.0
4	2b	7b	CH ₂ Cl ₂	room temp.	28 ^c	1.9
PhCH (Et) COOH (8)	5	9	CH ₂ Cl ₂	0°C	26 ^d	1.8

a Calculated from the specific rotation of *trans*-2, 4-dimethyl- δ -valerolactone yielded by the functional group selective reduction of **3b**.¹⁾b Determined on HPLC; $\alpha=1.10$; eluent, hexane: 2-propanol: Et₃N=30: 1: 0.1, flow 1.0 ml/min.c Determined on HPLC; $\alpha=1.03$; same the eluent as b, flow 2.5 ml/min.d Determined on HPLC; $\alpha=1.20$; eluent, hexane: 2-propanol: Et₃N=15: 1: 0.16, flow 2.0 ml/min.

was employed. The %de's and the ratios of k_A/k_B are given in Table 2. This simpler method can be applied for the rough estimation of selectivity on a reaction. It is also noted that the above method including the experiments at various ratios of N can offer useful information about the kinetic resolution. When the ratios of k_A/k_B calculated from ee's or de's of products at different N 's are extraordinarily inconsistent with each other, the fact may suggest that the reaction is not as simple as described in eq. 1.

EXPERIMENTAL

HPLC analysis was done on a Jasco BIP-1 chromatograph system equipped with a silica gel column; NUCLEOSIL 50-5, 4 mm \times 25 cm. Detection was carried out with absorbance at 280 nm. (*R*)-1-(1-Naphthyl)ethylamine was purchased from Tokyo Kasei Co. and distilled before use.

Typical procedure for kinetic resolution of acid anhydrides. Reaction of 1 with 2a: To 2a

Kinetic Treatment of Kinetic Resolution of Racemic Acid

(10 mg, 0.03 mmol) in toluene (2 ml), an amount of **1** specified in Table 1 was added at -20°C . After stirring at -20°C for 3 days, an ethereal solution of diazomethane was added to it. Without any purification,¹⁰ the product was analyzed on HPLC and the de of **3a** was determined based on the peak areas of the diastereomers.

Reaction of racemic 2-phenylbutyric acid (8) with 5: To a mixture of **8** (16.4 mg, 0.1 mmol) and 1-hydroxybenzotriazole hydrate (13.5 mg, 0.1 mmol) in dichloromethane (0.1 ml), DCC (20.6 mg, 0.1 mmol) in dichloromethane (0.1 ml) was added at 0°C . After stirring at 0°C for 1 hr, **5** (3.4 mg, 0.02 mmol) in dichloromethane (0.1 ml) was added to the solution. The mixture was stirred at 0°C for 1 hr and at room temperature overnight. Cyclohexylamine (9.9 mg, 0.1 mmol) in dichloromethane (1 ml) was added and the mixture was stirred at room temperature for 2 hr. After filtration, the product **9** was analyzed on HPLC.

ACKNOWLEDGMENT

This work was supported in part by a grant in aid (59760094) from the Ministry of Education of Japan to which we are deeply grateful.

REFERENCES AND NOTES

- (1) Y. Kawakami, J. Hirakake, Y. Yamamoto, and J. Oda, *J. Chem. Soc., Chem. Commun.*, 1984, 779.
- (2) J. Hiratake, Y. Yamamoto, and J. Oda, Submitted for publication in *J. Chem. Soc., Chem. Commun.*
- (3) The ratio of two rate constants of reaction paths yielding respective enantiomers is represented as $k_A/k_B = (1+ee)/(1-ee)$ in kinetic controlled reaction.
- (4) P. Newman, P. Rutkin, and K. Mislow, *J. Am. Chem. Soc.*, **80**, 465 (1958).
- (5) G. Balavoine, A. Moradpour, and H. B. Kagan, *ibid.*, **96**, 5152 (1974).
- (6) K. B. Sharpless *et al.*, *ibid.*, **103**, 6237 (1981).
- (7) C. S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *ibid.*, **104**, 7294 (1982).
- (8) In a region of $1 < N < 2$, **2a** is consumed incompletely.
- (9) F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, **123**, 663 (1923).
- (10) The structures of the amide-esters prepared here were confirmed by ^1H -NMR spectroscopy.